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Crosstalk between Endo/Exocytosis and Autophagy in Health and Disease

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Imbalance between the main intracellular degradative, trafficking and intercellular shuttling pathways has been implicated in disease pathogenesis. Autophagy controls degradation of cellular components, while vesicular trafficking permits transport of material in and out of the cell. Emerging evidence has uncovered the extensive interconnectivity between these pathways, which is crucial to maintain organismal homeostasis. Thus, therapeutic intervention and drug development strategies targeting these processes, particularly in neurodegeneration, should account for this broad crosstalk, to maximize effectiveness. Here, recent findings underlining the highly dynamic nature of the crosstalk between autophagy, endosomal transport, and secretion is reviewed. Synergy of autophagy and endosomes for degradation, as well as, competition of autophagy and secretion are discussed. Perturbation of this crosstalk triggers pathology especially neurodegeneration.

1. The Endo/Exosomal Pathway

Endocytosis mediates intracellular trafficking of cargo from outside of the cell. Potential cargo includes nutrients, microorganisms, and macromolecules such as lipids, receptor–ligand complexes, extracellular matrix, plasma membrane components, or vesicles derived from the plasma membrane. The mechanistic nature of material uptake varies, hence there are distinct endocytic pathways, which, nonetheless, merge at the stage of the early endosome.[1] Cargo can then be transported into intraluminal vesicles of late endosomes/multivesicular bodies (MVBs), which, in turn, fuse with the lytic organelle of the cell, the lysosome. Other possible routes require endosomal fission, and include sorting back to the cell surface, across polarized cells, through tubular extensions, as early endosomes, or delivery to the trans-Golgi network.[2] Thus, endosomal pathway(s) are key modulators of many cellular processes, by sorting, storing, degrading, recycling, activating, or suppressing material entering the cell.

Endocytic routes initiate at the plasma membrane, where endocytic vesicles are formed as a result of scission, followed by fusion with early endosomes. Endosomes constantly fuse with each other, via homotypic fusion, or with Golgi-derived vesicles. The balance of continuous endosome fusion and fission is essential for maintaining their membrane surface area, the recycling of membrane components and receptors back to the plasma membrane. Endosome degradation involves their maturation into late endosomes and subsequent fusion with the lysosome. Key effectors for this pathway are Rab guanosine triphosphate hydrolases (GTPases), soluble NSF attachment protein receptors (SNAREs), endosomal sorting complexes required for transport (ESCRTs) and clathrin coats. Transport of vesicles requires interaction with the cytoskeleton and contact of Rabs with the membrane of the target organelle. SNARE proteins found on both the vesicles and organellar membranes facilitate fusion. Ras-related protein 5 (Rab5), when activated by a Rab guanosine exchange factor at the plasma membrane, decorates vesicles and early endosomes, where it interacts with other proteins, such as early endosomal antigen 1 (EEA1) and phosphatidylinositol (PI)3-kinase vacuolar protein sorting 34 (Vps34), following its replacement by Rab7.[3] This protein is only found in more mature endosomes and can recruit either the retromer complex for transport to the Golgi, or Rab11 for return to the plasma membrane as recycling endosomes. The homotypic fusion and vacuole protein sorting (HOPS) tethering complex interacts with Rab7 to allow late endosomes to fuse with lysosomes or acquire lysosomal properties by taking up lysosome-associated membrane proteins (LAMPs), vacuolar H^+-ATPases for acidification and hydrolases for degradation.[4]

Exocytosis, on the other hand, is the delivery of material to the extracellular space. Exocytic events can be categorized according to the method cargo is transported outside: full collapse fusion, where vesicles collapse into the plasma membrane, "kiss-and-run," where the pore formed by fusion opens and closes, and compound exocytosis where vesicles fuse with each other to form larger extracellular structures, called exosomes. The process of exocytosis and secretion is largely coupled to endocytosis and vehicle retrieval.

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2. Autophagy

Autophagy, from the Greek words "auto," self, and "phagy," eating, is a physiological intracellular catabolic process which involves the degradation of macromolecules such as proteins, lipids, and organelles. It can be subdivided into macroautophagy, chaperone-mediated autophagy, and microautophagy. Here, we mainly focus on macroautophagy, henceforth called autophagy, which entails the formation of a double membrane vesicle that encloses and transports autophagic substrates to be degraded by fusion with the lysosome. Numerous studies have revealed the highly selective nature of autophagic processes, that do not merely serve bulk degradation purposes, as was originally thought.

Stress conditions such as starvation, hypoxic, oxidative, proteotoxic, or endoplasmic reticulum (ER) stress induce autophagy. Stepwise autophagy mechanisms initially entail the formation of a "crescent-shaped" phagophore, encompassing specific Atg proteins. Initially the autophagy induction complex Unc-51 like autophagy (ULK1)-ATG13-RB1-inducible coiled-coil protein 1 (RBCC1), is recruited to the isolation membrane. For nucleation of the phagophore, class III PI3K (PI3KC3) complex I, which consists of class III PI3K, VPS34, Beclin 1, autophagy-related protein/gene 14(ATG14), and activating molecule in Beclin 1-regulated autophagy protein 1 are activate to promote PI(3)P production on the membrane for omegasome formation. Then, two conjugation systems are required for phagophore expansion, which consist of first the ubiquitin-like microtubule-associated protein 1A/1B-light chain 3 (LC3) family, LC3A, LC3B, LC3C, and γ-aminobutyric acid type a (GABAA) receptor receptor-associated protein (GABARAP). Ubiquitin-like ATG12 conjugates with ATG5 and AT16L and in turn conjugate LC3 to phosphatidylethanolamine (PE) to form membrane bound LC3, LC3-II which is embedded on autophagic membranes.[5] Upon autophagosome–lysosome (autophagolysosome) fusion, the inner membrane, together with cargo constituents are degraded. Metabolites and other resultant molecules can then be used for anabolic processes.[6] Importantly, mature autophagosomes also fuse with late endosomes to form amphisomes that are then degraded in lysosomes. Recent experimental findings uncover the intricate relationships between the three processes that involve vesicular structures, namely autophagy, endosomes, and exosomes, and will be discussed further in this review.

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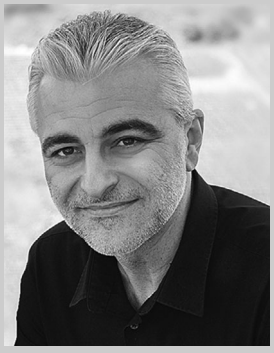

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3. Autophagy and Endo/Exocytosis Crosstalk

3.1. Interplay between Autophagy and Endocytosis

Endosomal components regulate the process of autophagy at multiple stages. First, the formation of the phagophore commences, derived from the omegasome, an early structure enriched in PI(3)Ps arising at the ER, and rapidly expands to become an autophagosome. Other sources of membranous structures for the formation of the double lipid bilayer of the autophagosome include vesicles from the plasma membrane, the Golgi, and mitochondria. A specific site for autophagosomal generation is between the ER and Golgi, the ER-Golgi intermediate compartment (ERGIC) where the coat protein complex II (COPII) machinery relocates and forms vesicles which act as membrane precursors for LC3 lipidation.[7] Specifically, after starvation, autophagy activates ULK1 which moves COPII protein Sec12 to the ERGIC, where enlargement of the ER exit sites (ERES) occurs, facilitated by RBCC1.[8] These vesicles then bud off and expand into phagophores. FBXW5 negatively modulates COPII-mediated autophagosome biogenesis under normal conditions.[9] Vesicles are transported from a donor site and delivered to an acceptor membrane, a process that also involves multiple components of the vesicular machinery, specifically clathrin that forms vesicle coats, Rab GTPases for activation and transfer, tether proteins to link the two membranous structures, and SNAREs to perform the fusion. Thus, early endosome vesicles resulting from endocytosis at the plasma membrane, coated with adaptor protein 2 (AP2), containing ATG16L and ATG9, fuse homotypically to form autophagosome precursor membranes via a vesicular soluble NSF attachment protein receptor.[10] In addition, vesicle COPII facilitates the lipidation of LC3, a critical component for autophagosomal structure and function Rab5 GTPase has emerged as a crucial factor for autophagosome formation and maturation. For example, Rab5

activates Vps34 to generate PI(3)P structures in early autophagic membranes.[11,12] Notably, recent live imaging experiments indicate that recycling endosomes are important contributors of autophagosome formation, together with ER-mitochondria contact sites, which were thought to be the sole autophagosome biogenesis sites.[13] Rab11 recycling endosomes act as platforms for early autophagosome formation, by generating PI(3)Ps, and WD repeat domain phosphoinositide-interacting protein 2, which recruit ATG16L to act as a docking site for LC3.[14] Thus, endosomal compartments are an integral component of the autophagic machinery for initiation of degradation.

Following, endosomal proteins are required for autophagosomal maturation and lysosomal fusion. In particular, Rab5, with the associated Vps21, activate Vps9 and, together with the class C core vacuole/endosome tethering complex (CORVET) and the Pep12 SNARE, seal the autophagosome.[15] Additionally, the ESCRT III subunit yeast Snf7, mammalian CHMP4 is essential for autophagosomal sealing.[16] Another ESCRT-III protein mammalian CHMP2A, with the aid of AAA-ATPase VPS4, moves to the phagophore and mediates the separation of the inner and outer autophagosomal membranes for autophagosomal formation.[17] Fusion of the autophagosome with the lysosome releases the single membrane autophagic body into the lysosomal compartment. This process requires membrane scission, which is triggered by the proteins mentioned above and mediated by the ESCRT. Rab7 regulates both autophagy and endocytosis, by recruiting phosphatidylinositol 4-phosphate at the stage of maturation, before their fusion with the lysosome.[18] Indeed, depletion of Rab7 in acute pancreatitis experimental mouse models causes autophagic flux perturbation and exacerbation of the pathological symptoms.[19] Elimination of the Rab7 effector EPG5 causes defects in the endosomal and autophagosomal pathway leading to a multisystem disorder called Vici syndrome.[20] Similarly, in *Drosophila*, Rab2 contributes to heterotypic fusion of late endosomes with lysosomes, and autophagosomes with the endo/lysosomal system, in addition to being involved in phagocytosis and secretion.[21] Syntaxins are utilized by both pathways for the supplementation of glycerophospholipids needed for fusion.[22] Recently, SNARE syntaxin17-positive autophagosome like structures have been demonstrated to form without the requirement of the ATG conjugation albeit at a slower rate than autophagosomes, and fuse with lysosomes, although a significant delay in the inner autophagosomal membrane degradation is observed.[23]Complementarity of the autophagic and the endocytic pathway two pathways is also conserved in phytopathogens, where Rab7 cooperates with Atg9.[24] Golgi reassembly-stacking protein of 55 kDa, a Golgi stacking protein, senses glucose deprivation by O-GlcNAcylation and acts as a tether by interacting with LC3 on autophagosomes and LAMP2 on late endosomes/lysosomes.[25] Notably, endosomes have also been implicated in the modulation of selective mitochondrial autophagy (mitophagy). The E3 ubiquitin ligase Parkin, a mitophagy mediator, together with the autophagy activator Beclin-1, engage the ESCRT machinery for the transfer of mitochondria to Rab5-positive endosomes that eventually fuse to lysosomes for degradation.[26] Consistently, the mitophagy receptor, BCL2-interacting protein 3, has also been found in endosomes.[27] Moreover, the ESCRT machinery proteins CHMP2A and CHMP4B are also required for phagophore closure in mitophagy and thus promote mitophagic flux.[28] Such extensive overlapping of the endosomal and mitophagic pathways contributes toward efficient mitochondrial recycling.

Endosomal microautophagy, by direct budding of endosome vesicles that are lysosomally degraded, without the involvement of autophagosomes, occurs after the first hours of amino acid starvation.[29] This form of microautophagy occurs after blockade of canonical selective macroautophagy to facilitate cell survival, while preparing for prolonged starvation by activating bulk, nonselective macroautophagy. Endosomal trafficking is vital for initiation of autophagosome formation. Sorting nexin 18 (SNX18) forms tubules from recycling endosomes for phagophore expansion and thus autophagosome biogenesis.[30] Atg9 transfer from the Golgi and recycling endosomes to sites of ATG16L1 and WD repeat domain, phosphoinositide interacting 1 (WIPI)-positive autophagosome formation during amino acid starvation, is mediated by the binding of membrane remodeling proteins SNX18 and dynamin 2.[31] Selective autophagy in yeast also requires sorting nexins, Snx4, and Atg20, which interact with ULK1 and Atg11, and bind to membranes containing PI(3)P to induce autophagy.[32] Autophagic degradation of the proteasome in yeast by coordination of Snx4 (Atg24), 41, and 42 occurs during nitrogen starvation, without the activation of nucleophagy.[33] Moreover, SNX4 is implicated in proper mitochondrial recycling quality control while its ablation causes premature aging.[34] The cytoplasm-to-vacuole (Cvt) selective autophagy pathway is regulated by the Arl3 and Arl1 GTPases, which, together with tethering factors, control trafficking of Atg9 to the Golgi.[35] The intricate nature of this cross-regulation is revealed in experimental models overexpressing the autophagic protein ATG16L1, where it aberrantly targets recycling endosomes.[36]

Autophagic and endosomal-mediated degradation appear to have common regulators, such as nuclear receptor binding factor 2, which mediates the degradation of amyloid precursor protein C-terminal fragments.[37] Accumulation of the C-terminal fragment C99 elicits endosomal enlargement and may contribute to memory impairment.[38] The transcription factor EB that controls expression of several autophagy genes, also modulates the endocytic pathway, and downstream mTOR signaling that impinges on both baseline and starvation-induced autophagy.[39]

Additional examples of autophagic proteins synergizing with endosomal components in non autophagic degradation and autophagosome trafficking have recently been reported in the literature. Moreover, a specific domain of ATG16L1, the C-terminal WD40 motif, is required for LC3 interaction, and consequently its lipidation and insertion into single membranes, during noncanonical autophagy The process of LC3-associated phagocytosis occurs when phagosomes and endosomes contain microorganisms, or apoptotic material to be degraded.[40] Furthermore, syntaxin 17 and the endosome-recruited motor protein dynein facilitate retrograde trafficking of autophagosomes back to the neuronal soma for amphisome formation and degradation.[41] Defects in this process have been implicated in neurodegeneration. Hence, perturbation of autophagy and endocytosis, two different but intertwined processes that act as checkpoints for intracellular organelle and protein quality control, contributes to the development of AD pathology.

Cross-regulation of endocytosis and autophagy allows for precise control of degradation processes during stress, to maintain

homeostasis. For example, during delayed implantation in mammalian embryonic development, autophagosomes and MVBs compete. Dormant blastocysts activate autophagy, but when the environment becomes favorable again, blastocysts and fibroblast growth factor (FGF) signaling induce MVB formation, possibly to clear waste generated by continuous autophagy.[42] Thus, the endosomal pathway restrains excessive autophagy. Complementarily, autophagy regulates plasma membrane receptor recycling by detecting damaged early endosomes and sorting them for degradation, thus promoting endosomal quality control.[43] Autophagy also allows cycling of the epidermal growth factor receptor (EGFR), via endosomes, back to the plasma membrane. Similarly, tumor necrosis factor receptor FGF-inducible 14 (Fn14) recycling is negatively regulated by distinct Atg8 proteins such as GABARAP, aided by the autophagy receptor p62.[44] Thus, autophagy impinges on TNFR function and recycling, further emphasizing the interdependence of the two pathways.

3.2. Interplay between Autophagy and Exosomes

The roles of autophagy have been expanded by recent findings, beyond the classical scope of lysosome-mediated degradation. LC3B transports interleukin 1β, to the extracellular space, through secretory autophagy. Moreover, ATG5 and ATG16L1 are crucial for exosome biogenesis.[45] In particular, ATG5 promotes the dissociation of vacuolar proton pumps from MVBs thereby blocking the acidification of the MVB lumen to allow for plasma membrane fusion and exosome release. Upon ATG5 perturbation, lysosomal or V-ATPase inhibitors restore exosomal release.[46] Under metabolic stress, autophagy is engaged to transport GLUT1 to the plasma membrane, facilitating glucose uptake and glycolytic flux by disinhibiting TBC1D5.[47] In lung epithelial cells, interferon-γ (IFN-γ), together with ATG5, induces engulfment of Annexin A2 by autophagosomes, which in turn fuse with MVBs for extracellular Annexin A2 secretion, required for efferocytosis, the engulfment of apoptotic cells.[48] Thus, autophagy is involved in the secretion of cytosolic proteins through a different mechanism from that of conventional secretion. However, it has been shown that autophagy supports conventional secretion as well and membrane protein transport to the plasma membrane.

Secretion and autophagy may also have competing roles. Starvation or rapamycin induce autophagy and autophagosome MVB fusion while hampering exosomal release.[49] Secretion can be blocked by a specific interferon stimulated gene 15 posttranslational modification (ISGylation) that targets MVBs for lysosomal degradation.[50] Also, serum deprivation increases secretion of the proteasomal 19S regulatory particle and noncanonical translation preinitiation complex components.[51] Recently, LC3B has been shown to co-localize with endosomal markers EEA1, RAB7, and RAB11 on amphisome-like structures which regulate reactive oxygen species production for mucin granule secretion.[52] Thus, the intricate interaction between autophagic and endo/exosomal compartments in autophagic as well as non-degradative roles requires further studies.

3.3. Disease-Related Pathology

Severing interconnections between these pathways has been associated to disease pathogenesis. ULK1 autophagy activator was shown to mediate Rab5 activation in the context of virus induced neurodegenerative disorders.[53] Another case is LC3-associated endocytosis that involves β-amyloid containing Rab5/clathrin positive endosomes (LANDO). LANDO facilitates β-amyloid aggregate clearance in microglia and alleviates neurodegeneration in a mouse model of Alzheimer's disease (AD).[54] Similarly, clearance of stressed mitochondria from axons is autophagy-independent and is mediated by syntaphilin, a mitochondrial anchoring protein, which is released from mitochondria into vesicles and late endosomes, in pathological conditions, such as amyotrophic lateral sclerosis (ALS) and AD. This likely occurs during the early stages of the disease, under lower stress levels, before activation of Parkin-mediated mitophagy.[55] In accordance with these findings, accumulation of genetic lesions affecting the autophagic and endolysosomal systems contributes to late onset AD.[56] Defects in dynein retrograde trafficking of autophagosomes back to the neuronal soma have been implicated in neurodegeneration. Deregulation of the ESCRT machinery such as Snf7-2 causes autophagosome accumulation, dendritic retraction, and ultimately neuronal loss.[57] Similarly, lack of ESCRT-0 causes aggregation of α-synuclein, TDP-43, and huntingtin.[58] Moreover lack of SNARE protein Snap29 causes autophagosomal accumulation, defects in membrane trafficking, cerebral dysgenesis, and neuropathy.[59] Upon lysosomal damage or overload, due to increased autophagosome production, in the context of neurodegenerative diseases caused by protein aggregation, exosomes release pre-lysosomal or lysosomal components to relieve stress.[60] Thus, instead of being degraded, toxic aggregates are released into the intercellular space, ultimately spreading the pathology to neighboring cells.[61] In genetic leukoencephalopathies, Vps11, which is a member of HOPS and CORVET, is mutated leading to decrease in central nervous system myelination.[62]

Apart from neurodegeneration-related disease, other pathologies arise affecting various tissues. Autophagy mediates insulin secretion in pancreatic β-cells through ATG7, thus, preventing hyperglycemia.[63] ATG5 and ATG16L1 facilitate exosomal release and promote metastasis by blocking endosomal acidification.[45] During liver fibrosis, the stress protein tribbles homolog 3 (TRIB3) that interacts with selective autophagy receptor p62, accumulates, blocking the interaction of p62 with LC3. As a consequence, autophagic flux is perturbed, and INHBA/activin A-enriched exosomes are secreted, inducing activation of hepatic stellate cells the effectors of liver fibrosis.[64] Degranulation of mast cells which instigates allergic reactions is promoted by the endosomal/autophagic pathways, thus targeting the pathway could prevent allergies.[65] Another immune pathology related to autophagy is Crohn's disease, where a combination of a virus infection and a mutation in a Crohn's susceptibility gene Atg16L1 together with environmental factors and commensal bacteria causes intestinal inflammatory disease in mice.[66] Body balance which is regulated by the ear, requires autophagy, for instance proteins LC3, Atg4b, and Atg5. Ablation of their function hinders otoconial core protein secretion and subsequently otoconial development. Defective equilibrioception

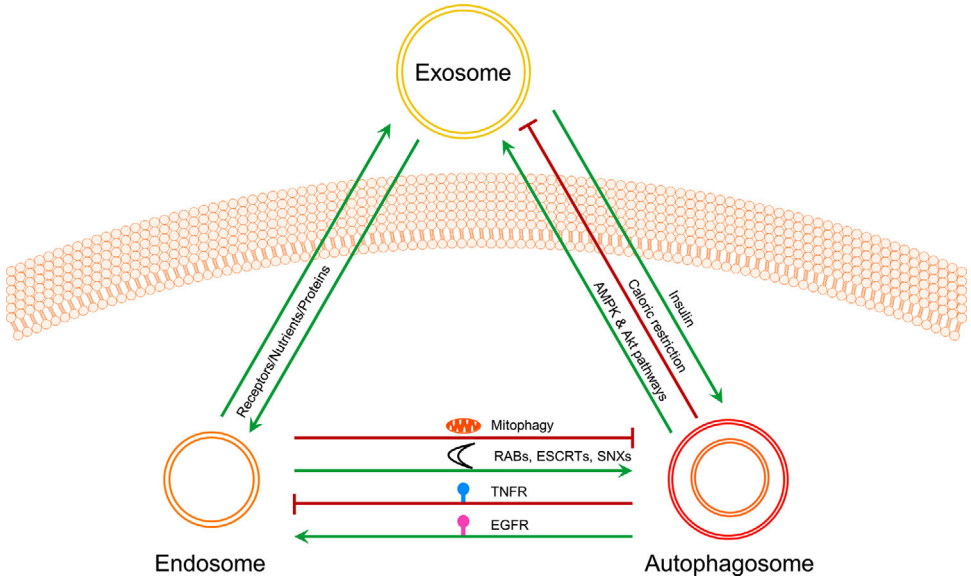

Figure 1. Cross-regulation of autophagy, endosomal and exosomal pathways. A simplified schematic diagram of the interactions between autophagy, endocytosis, and secretion is shown. Specific players are illustrated for each interaction. Endosomes and exosomes constantly interchange for nutrient and macromolecule transport. Tumor necrosis factor receptor (TNFR) Fn14 recycling is negatively regulated by the Atg8-related protein GABARAP, with the aid of the autophagy receptor p62. Autophagy allows shuttling of EGFR, via endosomes, to the plasma membrane. While, under caloric restriction, autophagy dampens exosomal release; under basal conditions it mediates insulin secretion in pancreatic β-cells, through ATG7. RABs and SNXs are required to form early autophagic structures and for autophagosomal maturation and degradation together with ESCRTs. Under mild stress, endosomes mediate mitochondrial degradation in lysosomes, independently of mitophagy. Exosomal release from mesenchymal stem cells (MSCs) elicits paracrine autophagic induction through the AMPK and Akt pathways.

Table 1. Links between autophagy and endo/exosomal pathways associated with disease pathogenesis.

Pathology	Pathway	Protein	References
Neurodegeneration	Axonal autophagosome transport	SNAP29, syntaxin 17, ESCRT-0, Snf7-2 (ESCRT-III)	[41,55–57]
AD/ALS	Mitophagy and endosomal trafficking	Dynein	[32]
Macular degeneration	Secretory autophagy	Atg9	[31]
Hyperglycaemia	Secretory autophagy	ATG7	[39]
Virus infection	Autophagy and endosomal trafficking	Rab5, Vps34	[12]
Acute pancreatitis	Endosomal/autophagosomal trafficking	Rab7	[19]
Vici syndrome	Endosomal/autophagosomal trafficking	Epg5	[20]
Liver fibrosis	Autophagic secretion	TRIB3-SQSTM1	[61]
Leukoencephalopathy	Autophagic secretion	Vps11	[60]
Human balance disorder	Autophagy and autophagic secretion	LC3B, ATG4B, ATG5	[64]
Allergy	Autophagic secretion	LC3	[62,63]
Crohn's disease	Autophagic secretion	ATG16L1 + virus	[63]
Osteoporosis	Autophagy and autophagic secretion	Beclin1, Atg5, Atg7, FIP200	[66]

which occurs in body balance disorders and the elderly population could be treated by autophagy activation.[67] Autophagy deficiency contributes to another age-related disease, osteoporosis, both by promoting osteoblast survival upon stress as well as their differentiation and mineralization, outward transportation of minerals. Therefore, coordination of autophagy and the endo/exosomal pathway permits effective intra and intercellular communication, while impairment of this synergy has been implicated in numerous pathologies such as macular degeneration during ageing.[35,68]

4. Conclusions and Future Perspectives

The notion that endocytosis, exocytosis, and autophagy are coupled, and to a large extend, overlap, is becoming increasingly appreciated (**Figure 1**). On the one hand, endosomes control multiple steps of autophagosomal initiation, maturation, and destruction. On the other hand, autophagy facilitates trafficking of endosomes. Autophagy has also been shown in several cases to promote secretion of specific receptors, while in others to impede it. This complementary, as well as competitive relationship

is tightly modulated under physiological conditions. However, the fine balance of cross regulation between these transport and degradative mechanisms is perturbed in disease, as shown in **Table 1**. Hence, the synergistic aspects of autophagy and endo/exocytosis provide intervention points for pharmacological interventions against related disorders. For example, inducing exosomal release from mesenchymal stem cells (MSCs) can rescue myocardial ischemia by inducing the adenosine monophosphate-activated protein kinase (AMPK) and Akt pathways, which in turn trigger autophagy.[69] Due to the promiscuity of the pathways involved, multifactorial diseases could potentially be battled by targeting a single effector. Consequently, autophagic and endo/exosomal mechanism intersection points could be exploited for the development of effective therapeutic approaches, relevant to multiple human pathologies.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

autophagy, endosome, exocytosis, neurodegenerative disorder, secretion

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